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Renal involvement in eosinophilic granulomatosis with polyangiitis

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), previously called Churg-Strauss syndrome, is a small to medium-sized systemic necrotizing vasculitis characterized by eosinophil-rich tissue infiltrates and granulomatous lesions. EGPA belongs to the larger subgroup of ANCA-associated vasculitides (AAV). However, EGPA is characterized by a distinct biological and clinical presentation when compared with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). EGPA is typically characterized by late onset asthma, nasal and sinus-related symptoms, peripheral neuropathy and prominent peripheral blood eosinophilia.[1] The prevalence of ANCA positivity in EGPA is about 40%, with predominant perinuclear staining, and exhibits an anti-MPO specificity in approximatively 65% of cases.[1,2] Unlike GPA and MPA, where kidney involvement is a central feature, nephropathy is not considered a prominent aspect in patients with EGPA.[1,3] For this reason, the nephrologist is not usually regarded as a key player in the care of EGPA patients. The case reported here dispels this misconception by demonstrating that, in selected cases, nephrological expertise may play an active role in patient management.

The Case

Clinical History and Laboratory Data at Presentation

A 63-year-old man was referred to our department for stage 3 KDIGO acute kidney injury. His preceding history was consistent for late-onset asthma, with initial symptoms occurring twenty years earlier, recurrent nasal polyposis with anosmia and uncomplicated type 2 diabetes. He had evidence of transient eosinophilia (blood eosinophil count: 1.4 x 10^9/l; normal range: 0.03–0.7) three years prior to his referral. Upon admission the patient reported fatigue, loss of weight and muscle weakness, predominantly in the lower limbs. In addition, he described nasal crusting obstruction.

Biological investigations showed eosinophilia (7.4 x 10^9/l) and stage 3 KDIGO acute kidney injury with a serum creatinine level of 360 μmol/l (normal range: 45–97), compared to 110 μmol/l twelve months earlier. The urine protein/creatinine ratio was 1.1 g/g (normal range: 0–30), with 0.6 g/g albuminuria. The patient presented with microscopic hematuria (urine RBC 113000/ml, normal range: <10000/ml). Anti-neutrophil cytoplasm antibodies (ANCA) were positive with perinuclear fluorescence (1/640, normal range: < 1/20). An enzyme-linked immunosorbent assay demonstrated elevated ANCA specific for myeloperoxidase (82 IU/ml, normal range: < 20).

Kidney Biopsy Specimen

The kidney biopsy showed seven glomeruli, four of which had active necrotizing glomerulonephritis, segmental fibrinoid necrosis and rupture of the glomerular basement membrane (Figure 1A). Interstitial fibrosis was moderate, with numerous foci of interstitial eosinophil polymorphonuclear leucocytes (Figure 1B). No interstitial granuloma was found. The specimen contained an

unremarkable artery. Immunofluorescence study yielded no deposit. Electron microscopy was not performed.

The diagnosis of eosinophilic granulomatosis with polyangiitis with renal involvement was proposed.

Treatment and Clinical Follow-up

The patient was treated with a pulse of methylprednisolone 500 mg daily for three days, followed by oral prednisone 1 mg/kg, intravenous cyclophosphamide 0.5 mg/m² (day 1, day 15, day 29 and then every 21 days for a total of 6 pulses). Seven sessions of plasmatic exchange over a 10-day period were initiated after the histopathological examination results were known. Hyper-eosinophilia receded from 7.4 x 10^9/l to 0.6 x 10^9/l the day after the initial steroid pulse. Peripheral blood eosinophilia had resolved four months after initial follow-up. Renal function improved gradually within ten days after the initiation of the induction treatment to reach a serum creatinine plateau of 140 µmol/l (estimated glomerular filtration rate of 46 ml/min/1.73m² according to the CKD-EPI formula). At final follow-up, residual proteinuria was still present, at around 1 g/g, whereas hematuria was not detected.

Discussion

Kidney disease ranks among the most prominent clinical characteristic of ANCA-associated vasculitis. Seventy percent of the patients with GPA display signs of renal involvement while it is a near-universal feature of patients with MPA. Nephrologists are perhaps less familiar with EGPA. However, intrinsic renal injury is in fact not uncommon, and has been recorded in up to 25% of patients affected by EGPA.[1,4]

As epitomized by the patient's history, EGPA typically follows three sequential stages. First, a prodromal phase characterized by atopic disease, allergic rhinitis and asthma, followed by a second eosinophilic phase defined by peripheral blood eosinophilia and eosinophilic infiltration of multiple organs and, lastly, a vasculitic stage marked by life-threatening systemic vasculitis affecting medium and small vessels. The prodromal phase usually precedes the vasculitic phase by approximately 10 years.[1,5] ANCA status represents the overriding determinant which dictates the clinical profile: ANCA-positive patients tend to display vasculitis-related symptoms including kidney disease and peripheral nerve involvement whereas ANCA-negative patients are more prone to develop complications in connection with eosinophilia.[2] Renal disease in EGPA is closely associated with ANCA positivity.[1,2,4] Indeed, patients with positive ANCA account for 80% of EGPA patients with renal involvement, although they represent less than 40% of all patients in most EGPA series.[1,4]

Necrotizing pauci-immune glomerulonephritis is the most common renal presentation, found in 88% of ANCA-positive EGPA cases with renal involvement.[4] Compared to MPA and GPA vasculitis, where kidney disease is frequently diagnosed at advanced stages, most EGPA patients with rapidly

progressive glomerulonephritis exhibit crescentic lesions, reflecting recent and acute insult. This pattern of renal injury may translate to an early recognition of renal disease heralded by demonstrative EGPA-associated extra-renal symptoms. More than half of EGPA biopsies displaying necrotizing crescentic glomerulonephritis also yielded prominent acute interstitial inflammation, mainly composed of eosinophilic polymorphonuclear cells. The interstitial inflammation is also a usual feature in GPA or MPA patients, but consists mainly of T- and B-lymphocytes, sometimes associated with plasma cells.[6] Inflammatory cells may also aggregate into granuloma, albeit very infrequently in an EGPA kidney biopsy, where it has been documented in only 5% of cases.[4] The case presented here encapsulates the histopathological hallmarks of renal involvement of the disease and serves as an illustration of the dual mechanisms of EGPA lesions whereby both eosinophilic organ infiltration (phase 2) and vasculitis with necrotizing glomerulonephritis are observed (phase 3). At any rate, acute kidney injury predicts poor prognosis and should warrant combined immunosuppressive therapy, typically an association of glucocorticoids and cyclophosphamide, to prevent the risk of severe chronic kidney disease (Figure 2).[7]

ANCA-negative EGPA patients seldom display renal involvement, yet atypical glomerular disease has recently been established. Durel *et al* documented cases of membranoproliferative and membranous nephropathy among ANCA-negative EGPA patients.[4] The coexistence of membranous nephropathy and EGPA could be more than an accidental finding considering both diseases may share a common genetic background with common HLA alleles involved in both EGPA and membranous nephropathy.[8] Moreover, ANCA-negative EGPA patients are characterized by a Th2-weighted pro-inflammatory response, akin to that of patients with membranous nephropathy.[8] Nevertheless, the connection between EGPA and membranous or membranoproliferative nephropathies needs to be substantiated by further studies.

This case, together with recent evidence, is at odds with a popular belief stemming from earlier works according to which renal disease in the context of EGPA is mild and follows a benign course.[9] Even if the diagnosis of renal disease is usually made early in EGPA, renal involvement is far from inconsequential, with nearly 20% of patients reaching end stage renal disease within four years of follow-up.[4] Renal vasculitis therefore remains a severe complication in all forms of AAV, and EGPA is no exception. A summary of learning points can be found in Table 1.

References

1. Comarmond C, Pagnoux C, Khellaf M, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum*. 2013;65(1):270-281. doi:10.1002/art.37721

2. Sinico RA, Di Toma L, Maggiore U, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum*. 2005;52(9):2926-2935. doi:10.1002/art.21250

3. Sinico RA, Di Toma L, Maggiore U, et al. Renal involvement in Churg-Strauss syndrome. *Am J Kidney Dis Off J Natl Kidney Found*. 2006;47(5):770-779. doi:10.1053/j.ajkd.2006.01.026

4. Durel C-A, Sinico RA, Teixeira V, et al. Renal involvement in eosinophilic granulomatosis with polyangiitis (EGPA): a multicentric retrospective study of 63 biopsy-proven cases. *Rheumatol Oxf Engl*. 2021;60(1):359-365. doi:10.1093/rheumatology/keaa416

5. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore)*. 1999;78(1):26-37. doi:10.1097/00005792-199901000-00003

6. Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol JASN*. 2010;21(10):1628-1636. doi:10.1681/ASN.2010050477

7. Groh M, Pagnoux C, Baldini C, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med*. 2015;26(7):545-553. doi:10.1016/j.ejim.2015.04.022

8. Kronbichler A, Bettac EL. Kidney disease in eosinophilic granulomatosis with polyangiitis: expect the unexpected. *Rheumatol Oxf Engl*. 2021;60(1):1-2. doi:10.1093/rheumatology/keaa571

9. Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine (Baltimore)*. 1984;63(2):65-81. doi:10.1097/00005792-198403000-00001

Table 1. Teaching points

- Eosinophilic granulomatosis with polyangiitis (EGPA) patients exhibit renal involvement in nearly a quarter of cases.
- The frequency of renal involvement and its histopathological manifestations is driven by ANCA status:
  - The great majority of EGPA patients with renal involvement are ANCA positive;
  - Necrotizing pauci-immune glomerulonephritis is the most common renal presentation in ANCA-positive EGPA;
  - Significant eosinophilic interstitial inflammation is found in half of the cases;
  - Renal involvement is infrequent in ANCA-negative EGPA and atypical renal presentation may occur.
- The course of renal disease in EGPA may be severe and should be managed accordingly.

Figures legends

Figure 1: **Kidney biopsy findings**

A. Active necrotizing glomerulonephritis showing fibrin deposits and segmental glomerular basement membrane rupture at light microscopy (original magnification x 400, Jones methenamine silver stain)
B. Eosinophil-rich interstitial inflammation at light microscopy (original magnification x 400, hematoxylin-eosin-saffron)

Figure 2: Summary of therapeutic options in EGPA according to disease severity

AZA: azathioprine, CYC: cyclophosphamide (intraveinous or oral), CNS: central nervous system, EGPA: eosinophilic granulomatosis with polyangiitis, ENT: ear nose throat, GC: glucocorticoids, IVIG: intraveinous immunoglobulins, MTX: methotrexate, PE: plasmapheresis, RTX: rituximab, RPGN: rapidly progressive glomerulonephritis

Five factor score is established by computing the algebraic sum related to each organ-related EGPA manifestation

Therapeutic options consistent with renal involvement appear in bold characters, question mark indicates treatment option that may be considered based on limited studies and/or ongoing studies.